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[Intervention Review]

Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

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ABSTRACT

Background

Intrauterine insemination (IUI) is a common treatment for couples with subfertility that does not involve the fallopian tubes. It is used to bring the sperm close to the released oocyte. Another method of introducing sperm is fallopian tube sperm perfusion (FSP). Fallopian tube sperm perfusion ensures the presence of higher sperm densities in the fallopian tubes at the time of ovulation than does standard IUI. These treatments are often used in combination with ovarian hyperstimulation.

Objectives

To compare intrauterine insemination versus fallopian tube sperm perfusion in the treatment of non-tubal subfertility, for live birth and pregnancy outcomes.

Search methods

We searched the Menstrual Disorders and Subfertility Group Trials Register, MEDLINE, CINAHL and EMBASE from inception to September 2013. We also searched study reference lists and trial registers.

Selection criteria

Randomised controlled trials (RCTs) comparing IUI with FSP in couples with non-tubal subfertility were included.

Data collection and analysis

Two review authors independently selected studies for inclusion, assessed study quality and extracted the data. If studies were sufficiently similar, data were combined using a fixed-effect model to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs). A random-effects model was used if substantial statistical heterogeneity was detected. Studies that included participants with unexplained or mixed (non-tubal) subfertility were analysed separately from studies restricted to participants with mild or moderate male factor subfertility. The overall quality of evidence for the main outcomes was summarised using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Main results

The review included 16 RCTs. Fourteen RCTs (1745 women) were included in the meta-analysis. Only three studies reported live birth per couple. No evidence of a statistically significant difference was noted between IUI and FSP in live birth (OR 0.94, 95% CI 0.59 to 1.49, three RCTs, 633 women, I^2 = 0%, low-quality evidence) or clinical pregnancy (OR 0.75, 95% CI 0.49 to 1.12, 14 RCTs, 1745 women, I^2 = 52%, low-quality evidence). These findings suggest that for a couple with a 13% chance of live birth using FSP, the chance when using IUI will be between 8% and 19%; and that for a couple with a 19% chance of pregnancy using FSP, the chance of pregnancy when using IUI will be between 10% and 20%. Nor was evidence found of a statistically significant difference between IUI and FSP in per-pregnancy of multiple pregnancy (OR 0.96, 95% CI 0.44 to 2.07, eight RCTs, 197 women, I^2 = 0%, low-quality evidence), miscarriage (OR 1.23, 95% CI 0.60 to 2.53, seven RCTs, 199 women, I^2 = 0%, low-quality evidence) or ectopic pregnancy (OR 1.71, 95% CI 0.42 to 6.88, four RCTs, 111 women, I^2 = 0%, very low quality evidence). Substantial heterogeneity was noted for the outcome of clinical pregnancy (I^2 = 54%), for which no clear explanation was provided.

Authors' conclusions

Currently no clear evidence suggests any difference between IUI and FSP with respect to their effectiveness and safety for treating couples with non-tubal subfertility. However, a high level of uncertainty is evident in the findings, and additional research may be useful.

PLAIN LANGUAGE SUMMARY

Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Review question: This review compared intrauterine insemination versus fallopian tube sperm perfusion in the treatment of non-tubal subfertility, for live birth and pregnancy outcomes.

Background: Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. Fallopian tube sperm perfusion (FSP) is a similar procedure that places sperm into the woman's fallopian tube, closer to the eggs than IUI. Both techniques aim to improve the chance of conception.

Study characteristics: The review included 16 randomised controlled trials (more than 1800 women) that compared these procedures for treating couples with non-tubal subfertility. Only three trials reported live birth. The evidence is current to September 2013. No trial reported its funding source, but one reported no conflict of interest, and one stated that it had received no commercial funding.

Key results: No clear evidence suggests any difference between IUI and FSP with respect to their effectiveness and safety in the treatment of couples with non-tubal subfertility. However, a high level of uncertainty due to lack of data is evident in the findings.

Quality of the evidence: The overall quality of the evidence was rated as low for most outcomes, largely because of the small quantity of available data.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

IUI compared with FSP for non-tubal infertility

Patient or population: women with non-tubal infertility
Settings: subfertility clinic
Intervention: intrauterine insemination
Comparison: fallopian tube sperm perfusion

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	FSP	IUI				
Live birth per couple	133 per 1000	126 per 1000 (83 to 186)	OR 0.94 (0.59 to 1.49)	633 (3 studies)	⊕⊕◯◯ low[1,2]	
Clinical pregnancy per couple	185 per 1000	145 per 1000 (100 to 202)	OR 0.75 (0.49 to 1.12)	1745 (14 studies)	⊕⊕◯◯ low[3,4]	
Multiple pregnancy per couple	70 per 1000	55 per 1000 (33 to 91)	OR 0.62 (0.29 to 1.32)	908 (7 studies)	⊕⊕◯◯ low[2,3]	
Miscarriage per couple	43 per 1000	46 per 1000 (24 to 84)	OR 1.07 (0.56 to 2.05)	884 (7 studies)	⊕⊕◯◯ low[2,3]	
Ectopic pregnancy per couple	10 per 1000	8 per 1000 (2 to 30)	OR 0.88 (0.24 to 3.19)	643 (4 studies)	⊕◯◯◯ very low[2,3,5]	

*The basis for the **assumed risk** (the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]One of the three studies did not describe method of allocation concealment and 19% of women in this study had mild tubal damage.
[2]Imprecision: Confidence intervals cross the line of no effect and do not exclude an appreciable benefit or harm.
[3]Most studies failed to provide adequate details of methods of sequence generation and allocation concealment.
[4]Unexplained statistical heterogeneity (I^2 = 52%).
[5]Very serious imprecision.

BACKGROUND

Description of the condition

Intrauterine insemination (IUI) is commonly offered to couples with types of subfertility not involving the fallopian tubes. Intrauterine insemination gained its popularity because it is a simple, non-invasive, cost-effective technique (Hughes 1997). It is usually combined with controlled ovarian hyperstimulation (COH).

Studies on the dynamics of sperm transport have found a progressive decline in the number of spermatozoa along the length of the female reproductive tract. In normal fallopian tubes, a maximum of only 200 spermatozoa are present in the ampulla (Mamas 1996). Ripps 1994 showed that the number of spermatozoa in the pouch of Douglas was very low after IUI. However, the number of spermatozoa could be significantly increased with utero-tubal flushes. On the other hand, some authors state that no correlation exists between the number of spermatozoa inseminated and subsequent pregnancy if at least one to five million spermatozoa are inseminated (Dodson 1991; van Weert 2004). With consideration of these observations, another simple non-invasive method was introduced, called *fallopian tube sperm perfusion*.

Traditional parameters for assessing the quality of human semen are the concentration, motility and morphology of sperm in the ejaculate. Reference values are based on observations in populations of healthy men, and absolute minimal values for each semen parameter are unknown (Lewis 2007). Since 1990, the World Health Organization (WHO) has published reference values with cut-off points indicative of male subfertility. The 1997 WHO criteria for male subfertility required at least one of the following: sperm concentration (sperm count) less than 20 million per milliliter, total motility less than 50% or normal morphology less than 50% (WHO 1987). Criteria have changed over time, with several revisions to these criteria, including changes in 1992, which reduced the cut-off for sperm morphology from 50% to 30% (WHO 1992). The 2010 WHO criteria include thresholds for sperm concentration of less than 15 million per milliliter, total motility less than 50% and normal morphology less than 4% (WHO 2010).

Description of the intervention

Semen (from the partner or the donor) is prepared to remove debris and to maximise the concentration of normal motile spermatozoa. Common methods of sperm preparation are the 'swim-up technique', whereby motile spermatozoa swim up into a culture medium, and the use of density gradients, which through centrifugation separate spermatozoa according to their density (Boomsma 2007).

Interuterine insemination involves placement of about 0.5 mL of inseminate into the uterine cavity, using a sterile, flexible catheter.

Fallopian tube sperm perfusion (FSP) is based on a pressure injection of 4 mL of sperm suspension while efforts are made to seal the cervix to prevent semen reflux. This ensures sperm flushing of the fallopian tubes and overflow of the inseminate into the pouch of Douglas (Fanchin 1995).

How the intervention might work

FSP was developed to promote higher sperm densities in the fallopian tubes at the time of ovulation than are provided with standard IUI.

However, a possible disadvantage of FSP is the large volume of inseminate, which may flush the ova out of the tubes or induce abnormal myosalpingeal contractions, resulting in expulsion of the ova from the tube and subsequent failure of fertilisation (Nuojua-Huttunen 1997).

Why it is important to do this review

Numerous published randomised controlled trials (RCTs) have compared the efficacy of FSP with that of standard IUI, and variable findings have been reported. Some of these studies did not have enough power to detect statistically significant differences; therefore it seemed appropriate to consider pooling the results. The aim of this review was to determine whether outcomes in improving the probability of conception differ between FSP and IUI. As one of the basic requirements for IUI, and subsequently FSP, is the presence of patent tubes, we investigated the efficacy of FSP and IUI in the treatment of non-tubal subfertility.

OBJECTIVES

To compare intrauterine insemination versus fallopian tube sperm perfusion in the treatment of non-tubal subfertility, for live birth and pregnancy outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished RCTs were eligible for inclusion. We excluded non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, participant numbers), as they are associated with a high risk of bias.

Cross-over trials were included, but we planned that only data from the first phase would be included in meta-analyses, as the cross-over design is not valid in this context.

Types of participants

Couples with non-tubal subfertility, including:

- couples with unexplained subfertility, defined as failure to conceive after trying for at least one year, with no abnormality found at a routine fertility checkup, or with other non-tubal causes of subfertility, such as mild endometriosis;
- couples with mild to moderate male subfertility, defined as semen quality not meeting the criteria for normality as defined by the WHO in 1987. For the first full review and the first update of the review, we used the 1987 definition of sperm normality (sperm concentration < 20×10^6/mL, or total motility < 50%, or normal morphology < 50%) to enable inclusion of studies performed before 1992, as well as more recent studies. In 2010 the WHO changed the criteria for concentration to < 15×10^6/mL; and
- couples with other non-tubal causes of subfertility (e.g. mild endometriosis).

Types of interventions

Trials comparing intrauterine insemination versus fallopian tube sperm perfusion were eligible for inclusion.

Types of outcome measures

Trials reporting at least one of the following outcomes were eligible for inclusion.

Primary outcome

- Live birth per couple.

Secondary outcomes

- Clinical pregnancy per couple (defined as evidence of a gestational sac, confirmed by ultrasound examination).
- Multiple pregnancy per couple.
- Miscarriage per couple.
- Ectopic pregnancy per couple.

Search methods for identification of studies

See Appendix 1; Appendix 2; Appendix 3; and Appendix 4 for search strategies.

We searched for all published and unpublished RCTs of FSP versus IUI, with no language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

We searched the following databases from inception to September 2013.

- Menstrual Disorders and Subfertility Group Trials Register. This register includes handsearching of all abstracts of meetings of the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology since 1987.
- MEDLINE.
- Cochrane Central Registry of Controlled Trials (CENTRAL).
- CINAHL.
- EMBASE.
- Trial registers for ongoing and registered trials (http://clinicaltrials.gov/ct2/home, http://www.who.int/trialsearch/Default.aspx).
- Conference abstracts and citations in the ISI Web of Knowledge (http://wokinfo.com/)
- OpenGrey for unpublished literature from Europe (http://www.opengrey.eu/)

Searching other resources

- We handsearched the reference lists of articles retrieved by the search.
- We contacted experts in the field.

Data collection and analysis

Selection of studies

An initial screen of titles and abstracts retrieved by the search was conducted by one review author (AEPC), and the full texts of all potentially eligible studies were retrieved. Four review authors (AEPC and MJH or CF or JM) independently selected the trials to be included according to the above-mentioned criteria. Disagreements were resolved through arbitration by a third review author (BJC). We corresponded with study investigators as required to clarify study eligibility.

Data extraction and management

Two review authors independently extracted data from eligible studies (AEPC and MJH; for the update CF and JM). Disagreements were resolved by discussion or by a third review author. Data extracted included study characteristics and outcome data (see Appendix 5). When studies had multiple publications, the main trial report was used as the reference, and additional details were derived from secondary papers. When important information was missing from the original publications, attempts were made to contact the primary investigators. Any additional information received was incorporated into this review.

Assessment of risk of bias in included studies

Two review authors independently assessed the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool (www.cochrane-handbook.org) to assess allocation (random sequence generation and allocation concealment); blinding of participants, personnel and/or outcome assessors; completeness of outcome data; selective reporting; and other potential sources of bias. Disagreements were resolved by discussion or by a third review author. We described all judgements fully and presented the conclusions in 'Risk of bias' tables.

Measures of treatment effect

All outcomes were dichotomous. We used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs). When data to calculate ORs were not available, we planned to utilise the most detailed numerical data available that might facilitate similar analyses of included studies (e.g. test statistics, P values).

Unit of analysis issues

The primary analysis was performed per woman randomly assigned for all outcomes.

We planned that data that did not allow valid analysis (e.g. "per cycle" data) would be briefly summarised in an additional table and would not be meta-analysed.

Multiple live births (e.g. twins, triplets) were counted as one live birth.

We planned to include only first-phase data from any cross-over trials.

Dealing with missing data

Data were analysed on an intention-to-treat basis as far as possible, and attempts were made to obtain missing data from the original trialists. When these data were unobtainable, imputation of individual values was undertaken for the primary outcome only: Live births were assumed not to have occurred in participants without a reported outcome. For other outcomes, only the available data were analysed.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I^2 statistic. An I^2 measurement greater than 50% was taken to indicate substantial heterogeneity (Higgins 2011). A random-effects model was used if heterogeneity was substantial.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the review authors aimed to minimise the potential impact of such biases by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If ten or more studies were included in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (i.e. the tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

If the studies were sufficiently similar, we combined them using a fixed-effect model to compare IUI versus FSP. An increase in the odds of a particular outcome, which might be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), is displayed graphically in the meta-analyses to the right of the centre-line, and a decrease in the odds of a particular outcome is displayed to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

We examined the effects of IUI versus FSP in the following subgroups, for the outcomes of live birth and clinical pregnancy.

- Participants with unexplained subfertility.
- Participants with mild or moderate male factor subfertility.

If we detected substantial statistical heterogeneity (I^2 measurement greater than 50%), we planned to explore possible explanations in sensitivity analyses based on other clinical or methodological differences between the studies.

Sensitivity analysis

We conducted sensitivity analyses for the outcome of clinical pregnancy to determine whether the conclusions were robust to arbitrary decisions made regarding study eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

- eligibility were restricted to studies with lower risk of bias (defined as studies with a low risk of bias related to randomisation and allocation concealment); or
- a random effects model had been adopted.

We also conducted sensitivity analyses for the outcomes of multiple pregnancy, miscarriage and ectopic pregnancy to determine whether our conclusions would have differed if the unit of analysis had been pregnancy rather than couple.

Overall quality of the body of evidence: 'Summary of findings' table

A 'Summary of findings' table was generated using GRADEPRO software. This table evaluated the overall quality of the body of

evidence for the main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) were incorporated into our interpretation of findings.

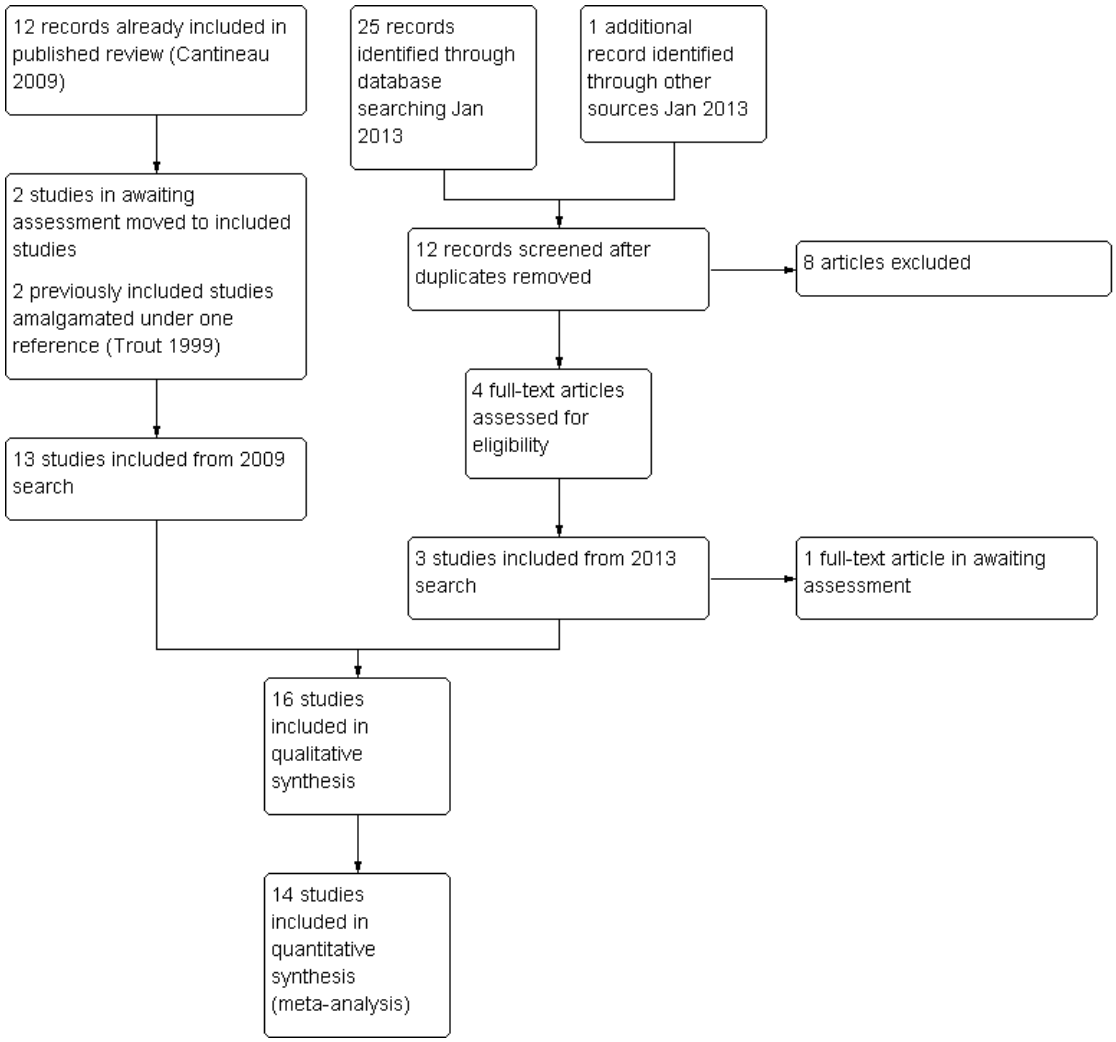
RESULTS

Description of studies

Results of the search

Eleven studies were included in the original review (published in 2004), and twelve in the 2009 update. Additional information was received from the authors of the following included studies: Biacchiardi 2004; Filer 1996a; Gregoriou 1995; Papier 1998, and the following excluded studies: Maheshwari 1998; Prietl 1999.
For the 2013 update, three new studies were added (El-Khayat 2012; Farquhar 2013; Furuya 2010), two studies previously classified as "awaiting assessment" were included (Kamel 1999; Noci 2007) and two previously included studies (Trout 1999 and Trout 1999 extension study) were amalgamated under a single reference. Therefore the review now includes 16 studies (Biacchiardi 2004; El-Khayat 2012; El Sadek 1998; Fanchin 1995; Farquhar 2013; Filer 1996; Furuya 2010; Gregoriou 1995; Kahn 1993; Kamel 1999; Ng 2003; Noci 2007; Nuojua-Huttunen 1997; Papier 1998; Ricci 2001; Trout 1999). In addition, one study is awaiting assessment (Ricci 2008).
Study flow is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

Design

The sample sizes of the 16 included studies ranged from 56 to 417 couples, where stated. One study of 106 cycles (Filer 1996) did not clearly state how many women were included. The other 15 studies included a total of 1855 women. Thirteen studies used a parallel-group design. The other three (Biacchiardi 2004; Filer 1996; Kamel 1999) used a cross-over design. Pre-cross-over data were available for Filer 1996 and Kamel 1999. Most were single-centre studies. Studies were conducted in tertiary institutions in Argentina, Denmark, Egypt, Finland, France, Greece, Hongkong, Italy ,Japan, New Zealand, Norway and the USA. None reported their funding source, but one reported no conflict of interest (El-Khayat 2012), and one stated that it had received no commercial funding (Ng 2003).

Participants

The mean or median duration of subfertility among participants in the included studies was about 3.5 years (range 2.0 to 4.4 years) in most studies. Two studies included women with a longer mean duration of subfertility (El Sadek 1998; Gregoriou 1995), and one (Trout 1999) did not state the mean duration of subfertility. Mean age of participants ranged from 29 to 36 years, where stated. In one study (Ng 2003), 24% of women had secondary subfertility.

The most common causes of subfertility in the included studies were unexplained infertility and male factor infertility. Other diagnoses included mild endometriosis, ovarian dysfunction and cervical factor. Two studies reported that although they excluded women with obstructed tubes (El Sadek 1998) and/or severely damaged tubes (Fanchin 1995), they included some with mild tubal damage. In El Sadek 1998, 19% of women had light peritubal adhesions or slightly reduced tubal fimbriae and/or moderate loss of gracility of the tubes. In Fanchin 1995, 37% of women had partial tube damage.

Two studies were restricted to couples with mild or moderate male factor infertility (El-Khayat 2012; Kamel 1999). In several other studies, a proportion of couples had mild male factor subfertility (when severity was reported): Ng 2003 (37%); Noci 2007 (19%); Nuojua-Huttunen 1997 (9%); Trout 1999 (16%); and Papier 1998 (proportion not stated).

Most studies included hysterosalpingography or laparoscopy to check tubal patency as part of the fertility investigative workup.

Interventions

1. Stimulation methods

Stimulation methods included the following:

- Clomiphene citrate (CC) alone or combined with human menopausal gonadotrophin (hMG), followed by one dose of human chorionic gonadotrophin (hCG): El Sadek 1998; El-Khayat 2012; Kahn 1993; Nuojua-Huttunen 1997; Kamel 1999;
- Follicle-stimulating hormone (FSH) plus one dose of hCG: Ricci 2001 (urinary FSH); Biacchiardi 2004 (recombinant FSH);
- hMG alone followed by one dose of hCG when the leading follicle was > 18 mm in diameter: Gregoriou 1995; Ng 2003; Papier 1998; and
- hMG or urinary FSH, plus one dose of hCG when leading follicle was > 18 mm and 2 others were > 16 mm (Noci 2007).

Two studies used a variety of stimulation protocols. Farquhar 2013 used no stimulation for 10% of women and used CC, FSH or letrozole for the remainder. Fanchin 1995 used hMG, FSH and/or gonadotrophin-releasing hormone agonist (GnRHa).

Two studies (Filer 1996; Furuya 2010) did not mention the type of stimulation used.

2. Semen preparation

When reported, studies used semen from the partner, except that 10% of cycles used donor sperm in Farquhar 2013. The volume of semen perfused for the FSP procedure was 4.0 mL in most studies. For the IUI technique, the volume of semen used varied between 0.2 mL and 1.0 mL.

Semen preparation methods included the following.

- Density gradient centrifugation techniques: Fanchin 1995; Farquhar 2013; Filer 1996; Gregoriou 1995; Ng 2003; Noci 2007; Nuojua-Huttunen 1997; Papier 1998; Trout 1999.
- Swim-up techniques: Biacchiardi 2004; El Sadek 1998; El-Khayat 2012; Kahn 1993; Kamel 1999; Ricci 2001.

One study (Furuya 2010) did not report the methods used for semen preparation.

3. Timing of intervention

Insemination or perfusion was between 34 and 42 hours after hCG in all trials. All studies performed a single insemination for both groups.

4. Catheters

Catheters used for IUI were as follows.

- Frydman: El Sadek 1998; Fanchin 1995; Kahn 1993; Kamel 1999; Noci 2007; Papier 1998; Ricci 2001.
- Tomcat: Ng 2003.
- Tomcat or Wallace: Farquhar 2013.
- Kremer de la Fontaine: Biacchiardi 2004; Nuojua-Huttunen 1997.
- Makler: Filer 1996; Gregoriou 1995.
- Conventional IUI canula: Trout 1999.
- Insulin syringe attached to an artificial insemination catheter: El-Khayat 2012.

Catheters used for FSP were as follows.

- Frydman with Allis clamp: El Sadek 1998; Gregoriou 1995; Kahn 1993; Kamel 1999.
- FAST system: Fanchin 1995; Ricci 2001.
- Foley catheter: Biacchiardi 2004; Nuojua-Huttunen 1997; El-Khayat 2012.
- Intrauterine injector with balloon: Ng 2003.
- Makler cannula: Filer 1996; Papier 1998.
- ZUII catheter with balloon: Trout 1999.
- Hysterosalpingography (Cervix Adaptor) catheter: Noci 2007.

One study (Furuya 2010) did not describe the catheters used.

5. Number of cycles

The maximum number of cycles included in the studies varied as follows.

- One cycle: Farquhar 2013; Nuojua-Huttunen 1997; Papier 1998.
- Three cycles: Furuya 2010; Gregoriou 1995; Kamel 1999; Kahn 1993; Ng 2003; Noci 2007; Ricci 2001.
- Four cycles: Biacchiardi 2004.
- Six cycles: Filer 1996.

Other studies (El-Khayat 2012; El Sadek 1998; Fanchin 1995; Trout 1999) did not report a maximum number of cycles per couple.

Outcomes

Primary outcome: live birth

Only three studies reported live birth (El Sadek 1998; El-Khayat 2012; Farquhar 2013).

Secondary outcomes

- Clinical pregnancy was reported by all studies. 'Per couple' data were reported by all but two studies (Fanchin 1995; Filer 1996), which reported only per-cycle data.
- Multiple pregnancy was reported by eight studies: El Sadek 1998; El-Khayat 2012; Fanchin 1995; Farquhar 2013; Kahn 1993; Ng 2003; Nuojua-Huttunen 1997; Ricci 2001.
- Miscarriage was reported by seven studies: El Sadek 1998; El-Khayat 2012; Farquhar 2013; Kahn 1993; Ng 2003; Nuojua-Huttunen 1997; Ricci 2001.
- Ectopic pregnancy was reported by four studies: El-Khayat 2012; Farquhar 2013; Kahn 1993; Ricci 2001.

For full details of the included studies, see Characteristics of included studies.

Excluded studies

Twenty-two studies were excluded because they did not perform the comparison of interest or were not randomised controlled trials: Allahbadia 1998; Arroyo Vieyra 1995; Ciftci 1998; Desai 1998; Dodson 1998; Elhelw 2000; Fanchin 1996; Fanchin 1997; Kahn 1992; Kahn 1992a; Kahn 1993a; Karande 1995; Levitas 1999; Li 1993; Maheshwari 1998; Mamas 1996; Mamas 2006; Posada 2005; Prietl 1999; Soliman 2005; Soliman 1999; Shekhawat 2012.
See Characteristics of excluded studies for details.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about all methodological quality items presented as percentages across all included studies.

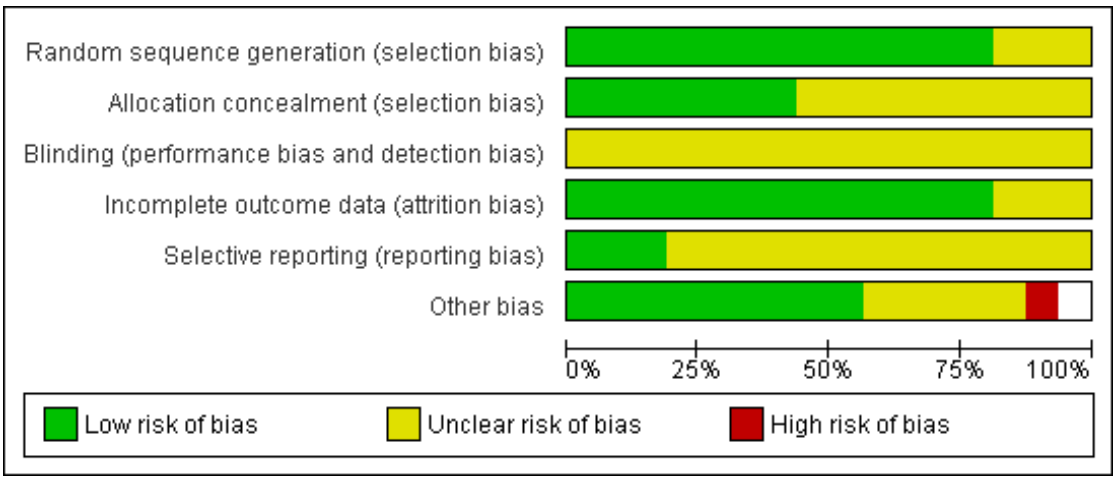
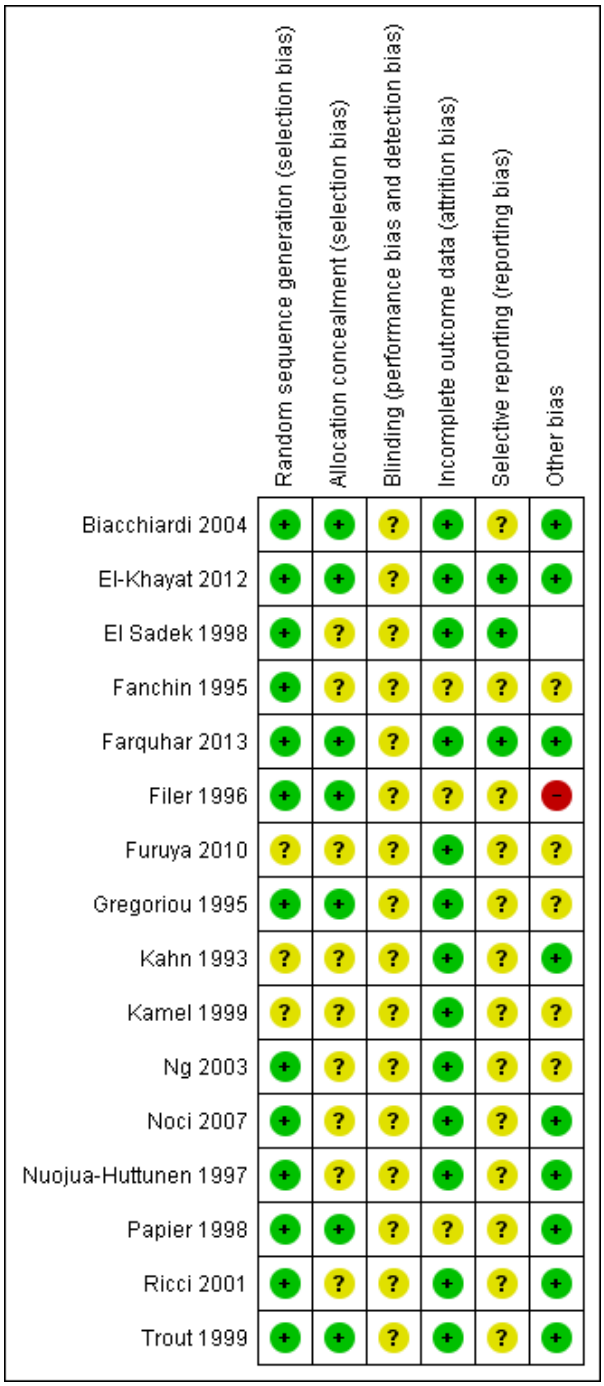


Figure 3. Methodological quality summary: review authors' judgements about all methodological quality items for each included study.



Allocation

Sequence generation

Thirteen studies reported adequate methods of sequence generation and were rated as at low risk of bias in this domain. The other three studies did not clearly describe their methods and were rated as at unclear risk of bias.

Allocation concealment

Seven studies reported adequate methods of allocation concealment and were rated as at low risk of bias in this domain. The other nine studies did not clearly describe their methods and were rated as at unclear risk of bias.

Blinding

Blinding was not reported in any of the studies. However, all studies were rated as at unclear risk of performance or detection bias, as it was uncertain whether blinding would influence the outcomes reported in this review.

Incomplete outcome data

Fourteen studies reported outcomes for all or nearly all randomly assigned participants and were rated as at low risk of attrition bias. In one study (Papier 1998),16% of women failed to receive the intervention, and another study (Fanchin 1995) did not report per-couple data: These two studies were rated as at unclear risk of attrition bias.

Selective reporting

Only three studies reported live birth (El Sadek 1998; El-Khayat 2012; Farquhar 2013). These studies were rated as at low risk of selection bias. The other studies failed to report live birth and in some cases also failed to report adverse events. These studies were rated as at unclear risk of selective reporting.

Other potential sources of bias

No other potential source of bias was identified in nine studies; these were rated as at low risk of bias. Limited information was available for two studies, as they were unpublished or were published only as abstracts (Furuya 2010; Kamel 1999). Two studies noted that the number of motile sperm inseminated differed between the groups (Gregoriou 1995; Ng 2003), and one study randomly assigned women but reported results per cycle (Fanchin 1995). Two studies included some women with mild tubal damage (El Sadek 1998; Fanchin 1995). These six studies were rated as at unclear risk of other bias. One study was rated as at high risk of bias because it used a cross-over design, which is not valid for studies reporting pregnancy outcomes, and no pre-cross-over data were available.

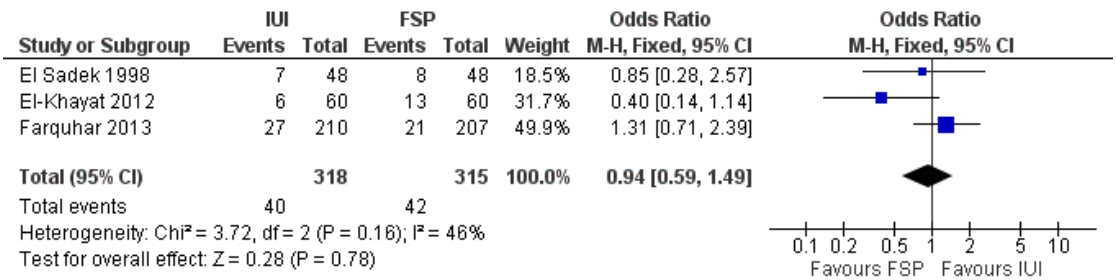
Effects of interventions

See: **Summary of findings for the main comparison** IUI compared with FSP for non-tubal infertility

Primary outcome: live birth per couple

Three studies reported this outcome. There was no evidence of a statistically significant difference between IUI and FSP (OR 0.94, 95% CI 0.59 to 1.49, three RCTs, 633 women, I^2 = 46%; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 NEW Intrauterine insemination versus fallopian tube sperm perfusion, outcome: 1.1 Live birth per couple.



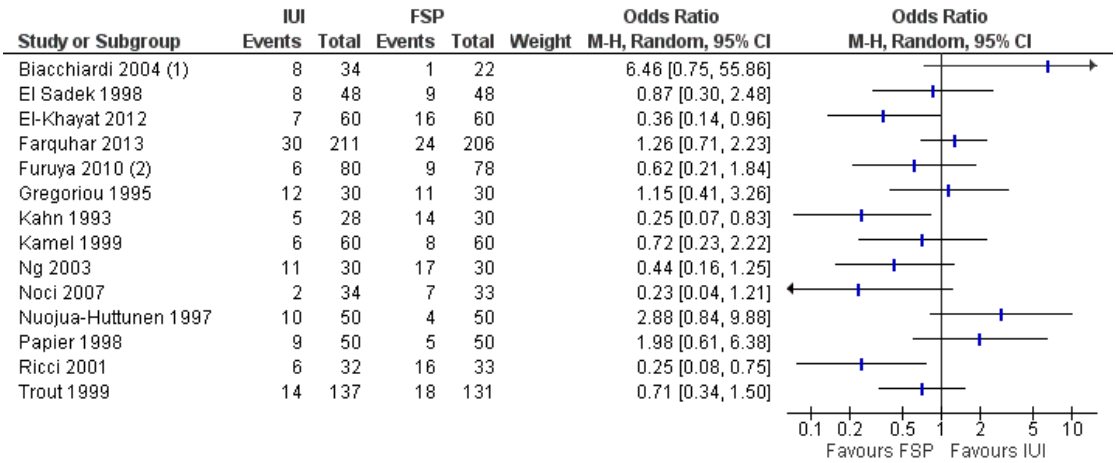
Secondary outcomes

1. Clinical pregnancy

Fourteen studies reported this outcome. There was substantial heterogeneity (I^2 = 52%), and so a random-effects model was used with no evidence of a statistically significant difference between IUI and FSP (OR 0.75, 95% CI 0.49 to 1.12, 14 RCTs, 1745 women, I^2 = 52%; Analysis 1.2; Figure 5)

We conducted sensitivity analyses, restricting the analyses to studies using similar methods of stimulation, similar catheter types and or similar methods of semen preparation (data not shown), but this did not explain the heterogeneity.

Figure 5. Forest plot of comparison: 1 IUI vs FSP: unexplained or mixed (non-tubal) causes, outcome: 1.2 Clinical pregnancy per couple (unexplained and mixed causes).



(1) Pre cross-over data
(2) 1st cycle only

One study of 74 couples (Fanchin 1995) reported only "per-cycle" data and so was not included in the meta-analysis (Table 1). The clinical pregnancy rate was significantly higher in the FSP group in this study (20% vs 40%; P < 0.04).

Sensitivity analysis using pregnancy as the unit of analysis also found no significant differences between groups (Analysis 1.3).

2. Multiple pregnancy

Seven studies reported this outcome. No evidence was found of a statistically significant difference between IUI and FSP (OR 0.62, 95% CI 0.29 to 1.32, seven RCTs, 908 women, I^2 = 0%; Analysis 1.3).

3. Miscarriage

Seven studies reported this outcome. No evidence was found of a statistically significant difference between IUI and FSP (OR 1.07, 95% CI 0.56 to 2.05, seven RCTs, 884 women, I^2 = 0%; Analysis 1.4).

Sensitivity analysis using pregnancy as the unit of analysis also found no significant differences between groups (Analysis 1.4).

4. Ectopic pregnancy

Four studies reported this outcome. No evidence was found of a statistically significant difference between IUI and FSP (OR 0.88, 95% CI 0.24 to 3.19, four RCTs, 643 women, I^2 = 0%; Analysis 1.5).

Sensitivity analysis using pregnancy as the unit of analysis also found no significant differences between groups (Analysis 1.5).

Subgroup analyses

1. Live birth and clinical pregnancy in couples with unexplained subfertility

No studies reported live birth in this subgroup.

Seven studies were restricted to couples with unexplained subfertility or reported separate statistical data on this group. When data were pooled, no evidence was found of a statistically significant difference in clinical pregnancy between the IUI group and the FSP group (OR 0.63, 95% CI 0.39 to 1.02, seven studies, 378 couples, I^2 = 66%). Heterogeneity for this analysis was high, for which there was no obvious explanation.

2. Live birth and clinical pregnancy in couples with mild or moderate male factor subfertility

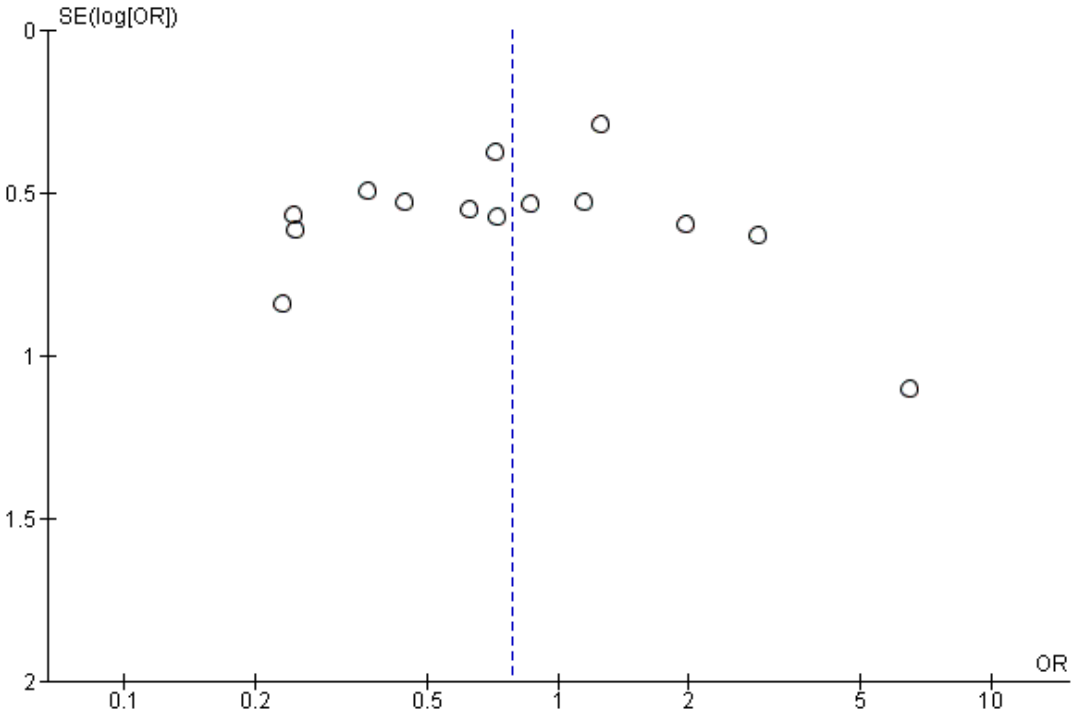
One study reported live birth in this subgroup. No evidence was found of a statistically significant difference between groups in live birth (OR 0.40, 95% CI 0.14 to 1.14, one study, n = 120).

Five studies were restricted to couples with male factor subfertility or reported separate statistical data for this group. When data were pooled, no evidence was found of a statistically significant difference in clinical pregnancy between the IUI group and the FSP group (OR 0.53, 95% CI 0.28 to 1.01, five studies, 303 couples, I^2 = 0%).

Assessment of reporting bias

A funnel plot for the outcome of clinical pregnancy was not suggestive of reporting bias (Figure 6).

Figure 6. Funnel plot of comparison: 1 IUI versus FSP, outcome: 1.2 Clinical pregnancy per couple.



Sensitivity analyses

Restriction to higher-quality studies or use of risk ratio rather than odds ratio did not substantially influence the overall findings for clinical pregnancy. In a post hoc sensitivity analysis, exclusion of the two studies in which some of the women had mild tubal damage did not influence the main findings.

DISCUSSION

Summary of main results

The aim of this review was to compare intrauterine insemination and fallopian tube sperm perfusion in the treatment of non-tubal subfertility, with respect to live birth, clinical pregnancy and adverse effects. No good evidence suggested any difference between IUI and FSP with respect to their effectiveness or safety in treating non-tubal subfertility. Findings suggest that for a couple with a 13% chance of live birth using FSP, the chance when using IUI will be between 8% and 19%; and that for a couple with a 19% chance of pregnancy using FSP, the chance of pregnancy when using IUI will be between 10% and 20%.

The evidence was of low quality. Moreover, the analyses of pregnancy rates appeared underpowered, with some suggestion of benefit for FSP.

We concluded that currently no good evidence suggests any difference between IUI and FSP with respect to their safety and effectiveness in treating non-tubal subfertility.

Overall completeness and applicability of evidence

A number of methodological considerations have to be considered when interpreting the results as clinical heterogeneity was noted in the included trials, as well as substantial statistical heterogeneity for the outcome of clinical pregnancy.

Types of subfertility differed between and within the trials and included unexplained subfertility, ovarian dysfunction, cervical factor, light peritubal adhesions, mild endometriosis and mild to moderate male factor subfertility.

Studies were similar with regard to mean participant age. Most studies excluded women over 39 years of age. Most fertility research centres have a maximum age of inclusion because of lower success rates with older women, related to lower ovarian reserve and oocyte quality in women over 40 years of age (Bukman 2000).

The duration of subfertility was at least one year in all of the studies (where reported) and was commonly longer than three years. It is known that fertility treatment is less successful with longer duration of subfertility.

The method of controlled ovarian hyperstimulation used varied among the included studies. Previous meta-analyses (Cantineau 2007; Crosignani 1996; Hughes 1997) have concluded that gonadotrophins are more effective than clomiphene citrate in the treatment of subfertile couples in IUI programmes. However, the largest included study (Dankert 2007) in Cantineau 2007 reported no statistically significant difference in effectiveness between CC and gonadotrophins. More aggressive ovarian stimulation is likely to increase pregnancy as well as multiple pregnancy and ovarian hyperstimulation syndrome (OHSS); this should be taken into account when study results are compared. In the current review, randomisation was done on the day of insemination after ovarian stimulation, so the ovarian stimulation method was unlikely to influence FSP and IUI outcomes.

Differing methods of sperm preparation were used and included both swim-up and gradient techniques. Use of a gradient might yield a higher recovery rate (Cohlen 1998), although a Cochrane review on recovery rates after different semen analysis techniques concluded that no semen preparation technique is superior to another (Boomsma 2007).

Differing catheters were also used. Different types of IUI catheters have been compared in a Cochrane review (van der Poel 2010), but no specific conclusion could be made regarding the superiority of one catheter class over another.

Quality of the evidence

The most common problems involving the quality of studies in this review were failure to report live birth as an outcome and failure to describe an acceptable method of allocation concealment. Most studies described acceptable methods of sequence generation and were at low risk of attrition bias or other sources of bias. One study reported only per-cycle data. All studies were apparently unblinded, but this was considered unlikely to cause bias.

As noted above, some analyses appeared underpowered.

Publication bias appeared unlikely, as a funnel graph for the outcome of clinical pregnancy was symmetrical (see Figure 6).

Using GRADE methods, the overall quality of the evidence was rated as low for all outcomes apart from ectopic pregnancy, for which it was rated as very low. This was largely a result of the small quantity of data available, which resulted in wide confidence intervals that were compatible both with no effect and with appreciable benefit or harm. In addition, most studies did not describe their methods in adequate detail. For the outcome of clinical pregnancy, substantial heterogeneity was noted, which was not adequately explained by clinical differences between the studies. See Summary of findings for the main comparison.

Potential biases in the review process

We are unaware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

No other reviews comparing fallopian tube sperm perfusion with intrauterine insemination are known to the review authors.

AUTHORS' CONCLUSIONS

Implications for practice

This review of 16 RCTs found no good evidence suggesting any difference between IUI and FSP with respect to safety and effectiveness in treating non-tubal subfertility. Findings suggest that for a couple with a 13% chance of live birth using FSP, the chance when using IUI will be between 8% and 19%; and that for a couple with a 19% chance of pregnancy using FSP, the chance when using IUI will be between 10% and 20%. Familiarity with one procedure may be more important than the technique itself.

Implications for research

Further RCTs in this area may be justified, as the current evidence appears underpowered. If such RCTs are undertaken, they should report live birth as an outcome, as well as clinical pregnancy and adverse effects, and should stratify participants by indication for treatment.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Biacchiardi 2004

Methods	Randomisation: blocked computer-generated sequence of numbers Trial design: cross-over Concealment of allocation: adequate
Participants	Participants: 56 women; 127 cycles Age of women: 33.2 ± 4.3 years for the total group Duration of subfertility: total group 2.4 ± 1.3 years Type of subfertility: unexplained subfertility (not further defined-mean duration of infertility 2.4 years)
Interventions	Stimulation method: rFSH 75 IU from CD 3 Intervention: IUI or FSP 35 to 37 hours after hCG, with husband's semen Semen preparation: swim-up Catheter used: IUI: Kremer de la Fontaine FSP: Foley catheter Maximum number of cycles per couple: 4
Outcomes	Clinical pregnancy per couple Multiple pregnancy Miscarriage
Notes	Additional details received from authors. Pre-cross-over data available

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated sequence of numbers blind to the operators
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pre-cross-over data reported for all randomised participants (n = 56)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported. OHSS not reported
Other bias	Low risk	No other potential source of bias noted

El Sadek 1998

Methods	Randomisation: block randomisation list Trial design: parallel Concealment of allocation: adequate
Participants	Participants: 96 women; 100 cycles Age of women: IUI 31.5 ± 5.3 years; FSP 32.0 ± 5.2 years Duration of subfertility: IUI 8.6 ± 2.1 years; FSP 7.3 ± 1.9 years Type of subfertility: unexplained subfertility, light peritubal adhesions*, PCO, cervical hostility *19% of participants with light peritubal adhesions or slightly reduced tubal fimbriae and/or moderate loss of gracility of the tubes. Women with obstructed tubes excluded
Interventions	Stimulation method: CC or CC + hMG + hCG Intervention: IUI or FSP 34 to 36 hours after hCG, with husband's semen Semen preparation: swim-up Catheter used: Frydman catheter (with Allis clamp for FSP) Maximum number of cycles per couple: not stated
Outcomes	Live birth Clinical pregnancy Multiple pregnancy Miscarriage
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Blocked randomization list"
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all randomised participants (n = 96)
Selective reporting (reporting bias)	Low risk	Reported live birth and adverse events

El-Khayat 2012

Methods	Randomisation: computer-generated random numbers Trial design: parallel Concealment of allocation: adequate
Participants	Participants: 120 women Age of women: mean 29 years Duration of subfertility: mean 3.4 to 3.6 years Type of subfertility: mild to moderate male factor infertility, defined as sperm count less than 15 × 106/mL, total motility less than 40% or normal forms less than 4%-per WHO criteria. Patients with severe oligospermia (<5 × 106/mL) excluded
Interventions	Stimulation method: CC + hMG Intervention: IUI or FSP 34 to 36 hours after hCG, with partner's semen Semen preparation: double-wash and swim-up Catheter used: insulin syringe attached to an artificial insemination catheter for IUI; pediatric Foley catheter for FSP Maximum number of cycles per couple: not stated
Outcomes	Clinical pregnancy (positive β-hCG test confirmed by ultrasound) Multiple pregnancy Miscarriage
Notes	Author sent data on allocation concealment and live birth by personal communication 4.4.13

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	"Closed sealed consecutively numbered opaque envelopes" (personal communication with author)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all randomised participants (n = 120)
Selective reporting (reporting bias)	Low risk	Reported live birth and adverse events
Other bias	Low risk	No other potential source of bias noted

Fanchin 1995

Methods	Randomisation: block randomisation list Power analysis: not stated Trial design: parallel Concealment of allocation: not stated
Participants	Participants: 74 women; 100 cycles Age of women: IUI 31.8 ± 4.6 years; FSP 31.8 ± 3.7 years Duration of subfertility: IUI 3.6 ± 1.2; FSP 3.4 ± 1.1 years Type of subfertility: partial tube damage*, idiopathic, cervical, ovulatory *37% of women with partial tube damage. Women with severe tubal damage or obstructed tubes excluded
Interventions	Stimulation method: (1) CC + hMG; (2) hMG alone; (3) FSH, hMG and GnRH agonist All followed by hCG Intervention: IUI or FSP 36 hours after hCG with husband's semen Sperm preparation: Percoll gradient Catheter used: Frydman catheter for IUI and FSP with FAST system Maximum number of cycles per couple: not stated
Outcomes	Pregnancy Multiple pregnancy Miscarriage
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Blocked randomisation list
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported for all cycles, but number of women in each group not reported
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Unclear risk	Unit of analysis error-women randomised, but data reported per cycle. 37% of women had mild tubal damage

Farquhar 2013

Methods	Randomisation: block randomisation list Trial design: parallel Concealment of allocation: serial numbered opaque sealed envelopes Pragmatic multicentred study design
Participants	Participants: 417 women; one cycle each Age of women: IUI 33.67 ± 4.87; FSP 34.23 ± 4.62 years Duration of subfertility: (median) IUI 24 (IQR 9 to 42); FSP 24 (IQR 11 to 36) months Type of subfertility: non-tubal infertility, 10% donor cycles
Interventions	Stimulation method: CC or FSH or letrozole (10% were unstimulated) Intervention: IUI or FSP 34 to 36 hours after hCG, with husband's semen IUI Catheter: Tomcat or Wallace catheter used for the IUI procedure. Inseminate prepared using a density gradient (Puresperm), and spermatozoa re-suspended in 0.5 mL of medium, as used in the recruiting centre. Catheter passed gently through the cervical canal high up into the uterus, and specimen with a volume of 0.5 mL slowly injected according to standard unit protocol FSP catheter: atraumatic insemination catheter (Cook catheter J-CHSG-503000) used for the FSP procedure Sperm preparation: inseminate prepared using a density gradient (Puresperm), and spermatozoa re-suspended in 4 mL of human tubal fluid or equivalent medium, as used in the recruiting centre. Catheter attached to a 5-mL syringe Maximum number of cycles per couple: one
Outcomes	Live birth Pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated randomisation sequence of random blocks of 3 different sizes, chosen randomly (with equal probability of getting 6, 8 or 10 in each block)"
Allocation concealment (selection bias)	Low risk	"Allocation numbers were placed in individual, sealed, opaque envelopes that were numbered sequentially"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding

Farquhar 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	6 withdrawals and 1 missing data
Selective reporting (reporting bias)	Low risk	No major protocol changes in outcomes
Other bias	Low risk	No other potential source of bias noted

Filer 1996

Methods	Randomisation: computer-generated algorithm Power analysis: not stated Trial design: cross-over Concealment of allocation: adequate
Participants	Participants: 106 cycles Age of women: < 40 years Duration of subfertility: at least one year Type of subfertility: unexplained
Interventions	Stimulation method: not stated Intervention: IUI or FSP 36 to 42 hours after hCG Sperm preparation: Percoll gradient Catheter used: Makler cannula for IUI and FSP Maximum number of cycles per couple: 6
Outcomes	Pregnancy
Notes	Additional details received from authors

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated algorithm
Allocation concealment (selection bias)	Low risk	After additional information from the author
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data reported per cycle only-number of couples not reported
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported

Filer 1996 (*Continued*)

Other bias	High risk	No pre-cross-over data reported. Limited information, as study available only as abstract

Furuya 2010

Methods	Randomisation: not stated Power analysis: not stated Trial design: parallel Concealment of allocation: not stated
Participants	Participants: 158 women, 322 cycles Age of women: not stated Duration of subfertility: not stated Type of subfertility: non-tubal infertility
Interventions	Stimulation method: not stated Intervention: IUI or FSP Sperm preparation: not stated Catheter used: not stated Maximum number of cycles per couple: 3
Outcomes	Pregnancy
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "they were randomised" ... no further details
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all randomised women (n = 158)
Selective reporting (reporting bias)	Unclear risk	Live birth and adverse effects not reported.
Other bias	Unclear risk	Limited reporting-abstract available only

Gregoriou 1995

Methods	Randomisation: list of random numbers Trial design: parallel Concealment of allocation: adequate
Participants	Participants: 60 women; 150 cycles Age of women: IUI 30.4 ± 3.5 years; FSP 30.3 ± 3.6 years Duration of subfertility: IUI 6.5 ± 2.1 years; FSP 6.3 ± 2.5 years Type of subfertility: unexplained subfertility Mean duration of unexplained infertility 6.5 years (range 2 to 12 years)
Interventions	Stimulation method: hMG 75 IU from CD 3 Intervention: IUI or FSP 36 hours after hCG with husband's semen Sperm preparation: two-layer Percoll gradient Catheter used: Makler device for IUI and Frydman catheter (with Allis clamp) for FSP Maximum number of cycles per couple: 3
Outcomes	Pregnancy
Notes	Additional details received from authors

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all women randomised (n = 60)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported, adverse effects not reported
Other bias	Unclear risk	Number of motile sperm inseminated was significantly higher in the FSP group

Kahn 1993

Methods	Randomisation method: not stated Trial design: parallel Concealment of allocation: sealed envelopes Power analysis: not stated
Participants	Participants: 60 women; 103 cycles Age of women: IUI 31.8 ± 0.8 years; FSP 31.7 ± 0.6 years Duration of subfertility: > 3 years Type of subfertility: unexplained infertility Minimum duration of unexplained infertility 3 years (range 3 to 6 years)
Interventions	Stimulation method: CC + hMG + hCG Intervention: IUI or FSP 34 to 37 hours after hCG with husband's semen Semen preparation: swim-up Catheter used: Frydman catheter (with Allis clamp for FSP) Maximum number of cycles per couple: 3
Outcomes	Clinical pregnancy per woman Multiple pregnancy Treatment complications Miscarriage
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The women were randomized for treatment with IUI or FSP on the day of HCG administration, by drawing a sealed envelope". No further details provided
Allocation concealment (selection bias)	Unclear risk	As above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for 58/60 women randomised (97%). Two women dropped out in IUI group-reasons explained
Selective reporting (reporting bias)	Unclear risk	Live birth not reported
Other bias	Low risk	No other potential source of bias noted

Kamel 1999

Methods	Randomisation method: not stated Trial design: cross-over Concealment of allocation: not reported
Participants	120 couples, moderate male factor infertility (not further defined)
Interventions	Stimulation method: CC 100 mg from day 3 to 8 when one follicle reached 18 mm Intervention: IUI with 0.5 mL of the sample or FSP 4 mL injected intrauterine under pressure after closure of the cervix with husband's semen Semen preparation: swim-up Catheter used: Frydman catheter (with Allis clamp for FSP) Maximum number of cycles per couple: 3 (on one treatment)
Outcomes	Pregnancy for pre-cross-over and post-cross-over data
Notes	Crossover: if no pregnancy occurred, method of insemination changed to that of the other group 3 months later

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "random cross-over study"-no further details
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for all women randomised (n = 120)
Selective reporting (reporting bias)	Unclear risk	Live birth and adverse effects not reported
Other bias	Unclear risk	Limited reporting-abstract available only

Ng 2003

Methods	Randomisation method: computer-generated randomisation list Trial design: parallel Concealment of allocation: not stated Follow-up: 3 cycles Power analysis: yes Intention-to-treat analysis: not performed
Participants	Participants: 90 women; 204 cycles (1) IUI 30 women, 68 cycles; (2) IUI 30 women, 76 cycles; and (3) FSP 30 women, 59 cycles Age of women: (1) IUI 32.7 ± 2.4 years; (2) IUI 32.9 ± 2.7 years Duration of subfertility: (1) IUI 4.4 ± 1.7; (2) IUI 4.2 ± 2.1 years 22/90 women had secondary infertility Type of subfertility: male factor (37%), unexplained subfertility and endometriosis Male subfertility not defined. All participants had > 10 million sperm in ejaculate during workup
Interventions	Stimulation method: 150 IU hMG from CD 3, dosage titrated later according to ovarian response; 10.000 IU hCG (1) IUI 38 hours after hCG; (2) FSP 38 hours after hCG; (3) IUI 18 and 38 hours after hCG with partner's semen (*Group 3 data not included in this review*) Sperm preparation: density gradient centrifugation method IUI procedure: 0.3 to 0.5 mL Tomcat catheter for IUI and intrauterine injectors (ZUOI-2) for FSP Maximum number of cycles per couple: 3
Outcomes	Clinical pregnancy per couple Miscarriage Multiple pregnancy
Notes	Luteal support with 1500 IU hCG on day 5 and day 10 after hCG

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomised women (n = 90)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported

Ng 2003 (*Continued*)

Other bias	Unclear risk	Total motile sperm count in first insemination significantly different between IUI group and FSP group

Noci 2007

Methods	Randomisation method: randomisation tables Trial design: three parallel arms-FSP, IUI and intraperitoneal insemination (IPI)-three cycles Concealment of allocation: not stated Power analysis: not stated Intention-to-treat analysis: not performed
Participants	Participants: 71 couples; 101 cycles (1) IUI 23 women, 34 cycles; (2) FSP 24 women, 33 cycles; and (3) IPI 24 women, 34 cycles *(Group 3 data not included in this review)* Age of women: (1) IUI 33.7 ± 1.6 2 years; (2) FSP 35.3 ± 3 years; and (3) IPI 35.3 ± 4. 4 years Duration of subfertility: (1) IUI 3.4 ± 1.6 years; (2) FSP 3.3 ± 1.9 years; and (3) IPI 3. 3 ± 1.4 years Type of subfertility: male (not further defined), unexplained subfertility; and endometriosis, mixed
Interventions	Stimulation method: recombinant or urinary FSH, dosage titrated later according to the ovarian response; 10,000 UI of hCG administered when 1 follicle > 18 mm and 2 others > 16 mm Sperm preparation: discontinuous density gradient centrifugation method (PureSperm) IUI procedure: Frydman catheter 0.3 to 0.5 mL FSP using a hysterosalpingography (Cervix Adaptor) catheter IPI: direct 2 mL sperm preparation injected into posterior vaginal fornix by a 19-gauge 2.2-cm needle Maximum number of cycles per couple: 3
Outcomes	Clinical pregnancy Multiple pregnancy
Notes	*All pregnancies occurred on first cycle*

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Couples were randomized by predefined tables of randomization"
Allocation concealment (selection bias)	Unclear risk	No details reported

Noci 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomised participants (n = 71)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported. Miscarriage not reported
Other bias	Low risk	No other potential source of bias noted

Nuojua-Huttunen 1997

Methods	Randomisation: computer-generated random numbers Trial design: parallel Concealment of allocation: not stated Power analysis: yes
Participants	Participants: 100 women; 100 cycles Age of women: IUI 31.1 ± 4.0 years; FSP 30.2 ± 4.4 years Duration of subfertility: IUI 3.8 ± 2.2 years; FSP 2.9 ± 1.7 years Type of subfertility: male subfertility, unexplained subfertility, mild endometriosis, ovarian dysfunction Duration of unexplained infertility not reported Male subfertility defined as sperm quality before treatment normal or slightly abnormal (> 10×10^6 sperm per mL, > 40% progressive motility [grade A + B], > 30% normal forms and after a Percoll preparation > 1×10^6 progressively motile sperm per mL)
Interventions	Stimulation method: CC + hMG + hCG Intervention: FSP or IUI 36 hours after hCG, type of semen not stated Semen preparation: Percoll gradient Catheter used: Kremer de la Fontaine for IUI; Foley catheter for FSP Maximum number of cycles per couple: 1
Outcomes	Clinical pregnancy per woman Multiple pregnancy Miscarriage OHSS
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Nuojua-Huttunen 1997 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomised participants (n = 100)
Selective reporting (reporting bias)	Unclear risk	Live birth not reported
Other bias	Low risk	No other potential source of bias noted

Papier 1998

Methods	Randomisation: computer-generated random numbers Trial design: parallel Concealment of allocation: adequate Power analysis: no
Participants	Participants: 100 women; 87 cycles Age of women: not stated Duration of subfertility: at least one year Type of subfertility: mild male subfertility, unexplained subfertility
Interventions	Stimulation method: hMG from CD 5 + hCG Intervention: FSP 34 hours after hCG and IUI 38 hours after hCG; type of semen not stated Semen preparation: Percoll gradient Catheter used: Frydman for IUI; Makler cannula for FSP Maximum number of cycles per couple: 1
Outcomes	Pregnancy
Notes	Luteal support with 400 mg progesterone. Additional details received from authors

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Adequate

Papier 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16 participants did not undergo intervention (reasons given), but intention to treat analysis possible (assuming no pregnancy in those 16 women)
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Low risk	No other potential source of bias noted

Ricci 2001

Methods	Randomisation: random number generator on computer Trial design: parallel Concealment of allocation: not stated Power analysis: yes
Participants	Participants: 65 women; 132 cycles Age of women: IUI 34.8 ± 4.6 years; FSP 35.5 ± 3.5 years Duration of subfertility: IUI 3.5 ± 1.4 years; FSP 3.4 ± 1.3 years Type of subfertility: unexplained infertility for 2 years
Interventions	Stimulation method: u-hFSH + hCG Intervention: IUI and FSP 36 hours after hCG with husband's semen Semen preparation: swim-up Catheter used: Frydman catheter for IUI; FAST system for FSP Maximum number of cycles per couple: 3
Outcomes	Ongoing pregnancy Multiple pregnancy
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator on computer
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported

Ricci 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Low risk	No other potential source of bias noted

Trout 1999

Methods	Randomisation: random number generator Trial design: parallel Concealment of allocation: third party Power analysis: yes
Participants	Participants: 268 women; 268 cycles Age of women: IUI 33.0 ± 2.7 years; FSP 33.0 ± 2.5 years Duration of subfertility: not stated Type of subfertility: ovulation dysfunction, unexplained infertility, male factor, endometriosis, cervical mucus factor, multiple diagnosis
Interventions	Stimulation method: CC + gonadotropins or gonadotropins alone + hCG Intervention: IUI or FSP 36 hours after hCG with husband's semen Semen preparation: Percoll gradient Catheter used: IUI catheter for IUI; ZUI II catheter for FSP Maximum number of cycles per couple: not stated
Outcomes	Clinical pregnancy Ectopic pregnancy
Notes	Duration of infertility unknown

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	States, "Neither the physicians enrolling the patients nor the physicians performing the inseminations had access to the randomization schedule"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding reported

Trout 1999 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all women who received interventions, but does not clearly state how many women randomised, so unclear whether any dropped out
Selective reporting (reporting bias)	Unclear risk	Does not report live birth, miscarriage or OHSS
Other bias	Low risk	No other potential source of bias noted

CC = clomiphene citrate.
FSH = follicle-stimulating hormone.
FSP = fallopian sperm perfusion.
GnRH = gonadotrophin-releasing hormone.
hMG = human menopausal gonadotropin.
IUI = intrauterine insemination.
LBR = live birth rate.
OHSS = ovarian hyperstimulation syndrome.
PR = pregnancy rate.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allahbadia 1998	Randomisation method was not stated, and the groups were not equal (369 in IUI group and 20 in FSP group), which makes adequate randomisation impossible. The author did not reply to our request for further information. Duration of subfertility was not stated
Arroyo Vieyra 1995	Randomisation method was not stated, and the groups were not equal (95 cycles with IUI and 36 cycles with FSP), which makes adequate randomisation improbable. The author did not reply to our request for further information
Ciftci 1998	The trial was quasi-randomised. The duration of subfertility was not stated. The author gave additional information regarding data after the first cycle. However, these data consisted of only pregnancies per cycle. Moreover, no data were available on the duration of subfertility
Desai 1998	Randomisation method was not stated, but the groups were not equal (369 in IUI group and 20 in FSP group), which makes adequate randomisation improbable. The author did not reply to our request for further information. The duration of subfertility was not stated
Dodson 1998	The trial did not perform the comparison of interest
Elhelw 2000	Letter Publication did not perform the comparison of interest

(*Continued*)

Fanchin 1996	Letter Publication did not perform the comparison of interest
Fanchin 1997	Letter Publication did not perform the comparison of interest
Kahn 1992	Cohort study
Kahn 1992a	Cohort study
Kahn 1993a	This study did not perform the comparison of interest
Karande 1995	Both IUI and FSP were performed on two consecutive days after hCG administration. A substantial number of women with tubal subfertility were included. The duration of subfertility was not stated
Levitas 1999	This study did not perform the comparison of interest
Li 1993	Case report that described a simple non-invasive method of fallopian tube sperm perfusion. This study did not perform the comparison of interest
Maheshwari 1998	The trial was quasi-randomised
Mamas 1996	The trial was quasi-randomised
Mamas 2006	The trial did not perform the comparison of interest. Intrauterine tuboperitoneal insemination is not the same as fallopian tube sperm perfusion
Posada 2005	The trial did not perform the comparison of interest
Prietl 1999	This study compared conventional IUI with intra-tubal insemination, which is different from perfusion of the fallopian tubes (FSP)
Shekhawat 2012	The method of allocation was not random and used odd and even numbers of the ART register to assign FSP and IUI. Confirmed in writing by author
Soliman 1999	The trial was a non-controlled randomised trial
Soliman 2005	The trial did not perform the comparison of interest

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ricci 2008

Methods	RCT
Participants	400 couples with unexplained or mild male factor infertility
Interventions	IUI versus FSP in natural cycles
Outcomes	Clinical pregnancy, ectopic pregnancy, miscarriage
Notes	Study completed December 2009. Emailed lead investigator March 2013-no response to date

DATA AND ANALYSES

Comparison 1. IUI versus FSP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth per couple	3	633	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.49]
2 Clinical pregnancy per couple	14		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3 Multiple pregnancy	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Multiple pregnancy per couple	7	908	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.29, 1.32]
3.2 Sensitivity analysis: multiple pregnancy per pregnancy	8	197	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.44, 2.07]
4 Miscarriage rate	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Miscarriage per couple	7	884	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.56, 2.05]
4.2 Miscarriage per pregnancy	7	180	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.63, 2.78]
5 Ectopic pregnancy	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Ectopic pregnancy per couple	4	643	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.24, 3.19]
5.2 Ectopic pregnancy per pregnancy	4	111	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.42, 6.88]

Comparison 2. IUI versus FSP subgroups by indication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Unexplained subfertility	7	378	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.39, 1.02]
1.1 Clinical pregnancy	7	378	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.39, 1.02]
2 Mild to moderate male factor subfertility	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Live birth	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.14, 1.14]
2.2 Clinical pregnancy	5	303	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 1.01]

Analysis 1.1. Comparison 1 IUI versus FSP, Outcome 1 Live birth per couple.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 IUI versus FSP

Outcome: 1 Live birth per couple

Study or subgroup	IUI n/N	FSP n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
El Sadek 1998	7/48	8/48		18.5 %	0.85 [0.28, 2.57]
El-Khayat 2012	6/60	13/60		31.7 %	0.40 [0.14, 1.14]
Farquhar 2013	27/210	21/207		49.9 %	1.31 [0.71, 2.39]
Total (95% CI)	**318**	**315**		**100.0 %**	**0.94 [0.59, 1.49]**

Total events: 40 (IUI), 42 (FSP)

Heterogeneity: $Chi^2 = 3.72$, df = 2 (P = 0.16); $I^2 = 46\%$

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

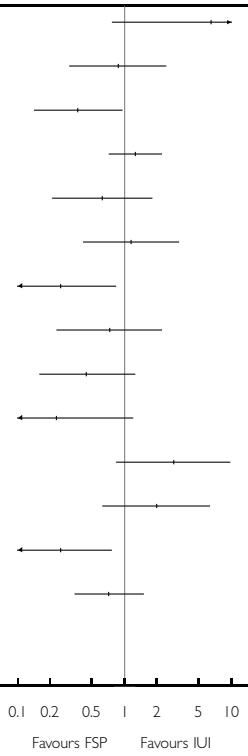
Analysis 1.2. Comparison 1 IUI versus FSP, Outcome 2 Clinical pregnancy per couple.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 IUI versus FSP

Outcome: 2 Clinical pregnancy per couple

Study or subgroup	IUI n/N	FSP n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Biacchiardi 2004 (1)	8/34	1/22			6.46 [0.75, 55.86]
El Sadek 1998	8/48	9/48			0.87 [0.30, 2.48]
El-Khayat 2012	7/60	16/60			0.36 [0.14, 0.96]
Farquhar 2013	30/211	24/206			1.26 [0.71, 2.23]
Furuya 2010 (2)	6/80	9/78			0.62 [0.21, 1.84]
Gregoriou 1995	12/30	11/30			1.15 [0.41, 3.26]
Kahn 1993	5/28	14/30			0.25 [0.07, 0.83]
Kamel 1999	6/60	8/60			0.72 [0.23, 2.22]
Ng 2003	11/30	17/30			0.44 [0.16, 1.25]
Noci 2007	2/34	7/33			0.23 [0.04, 1.21]
Nuojua-Huttunen 1997	10/50	4/50			2.88 [0.84, 9.88]
Papier 1998	9/50	5/50			1.98 [0.61, 6.38]
Ricci 2001	6/32	16/33			0.25 [0.08, 0.75]
Trout 1999	14/137	18/131			0.71 [0.34, 1.50]
Test for subgroup differences: Not applicable					



(1) Pre cross-over data

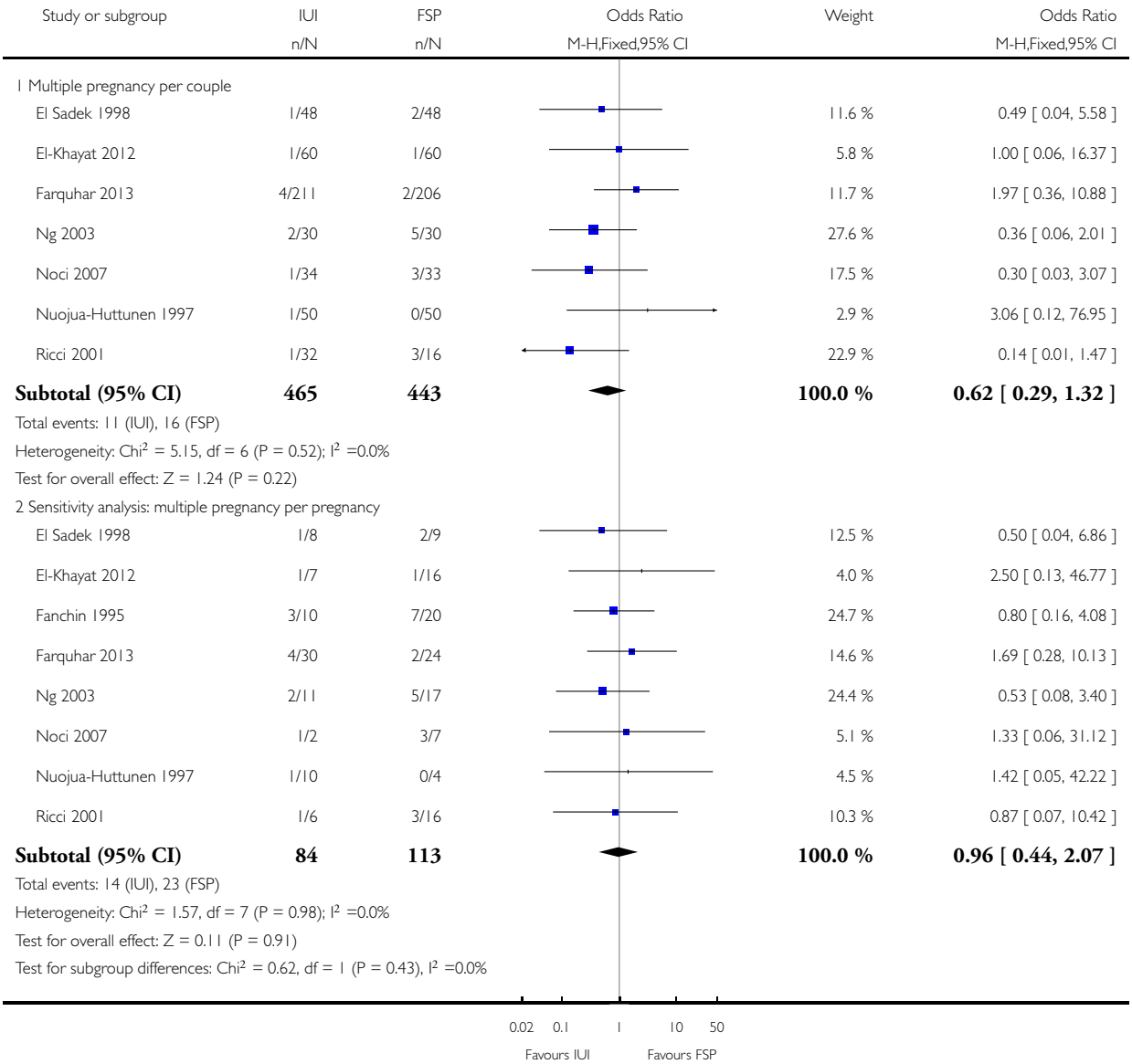
(2) 1st cycle only

Analysis 1.3. Comparison 1 IUI versus FSP, Outcome 3 Multiple pregnancy.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 IUI versus FSP

Outcome: 3 Multiple pregnancy

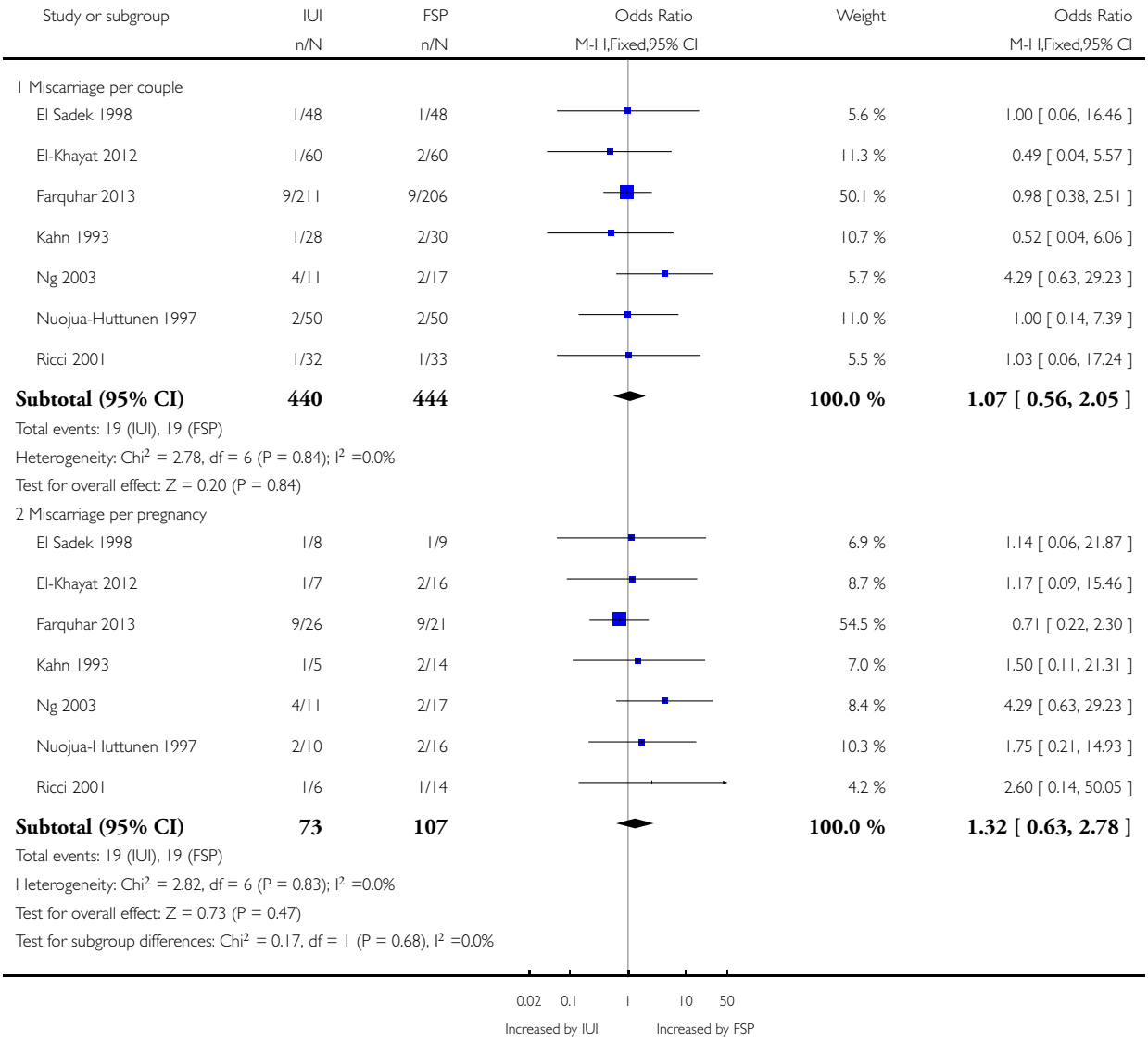


Analysis 1.4. Comparison 1 IUI versus FSP, Outcome 4 Miscarriage rate.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 IUI versus FSP

Outcome: 4 Miscarriage rate

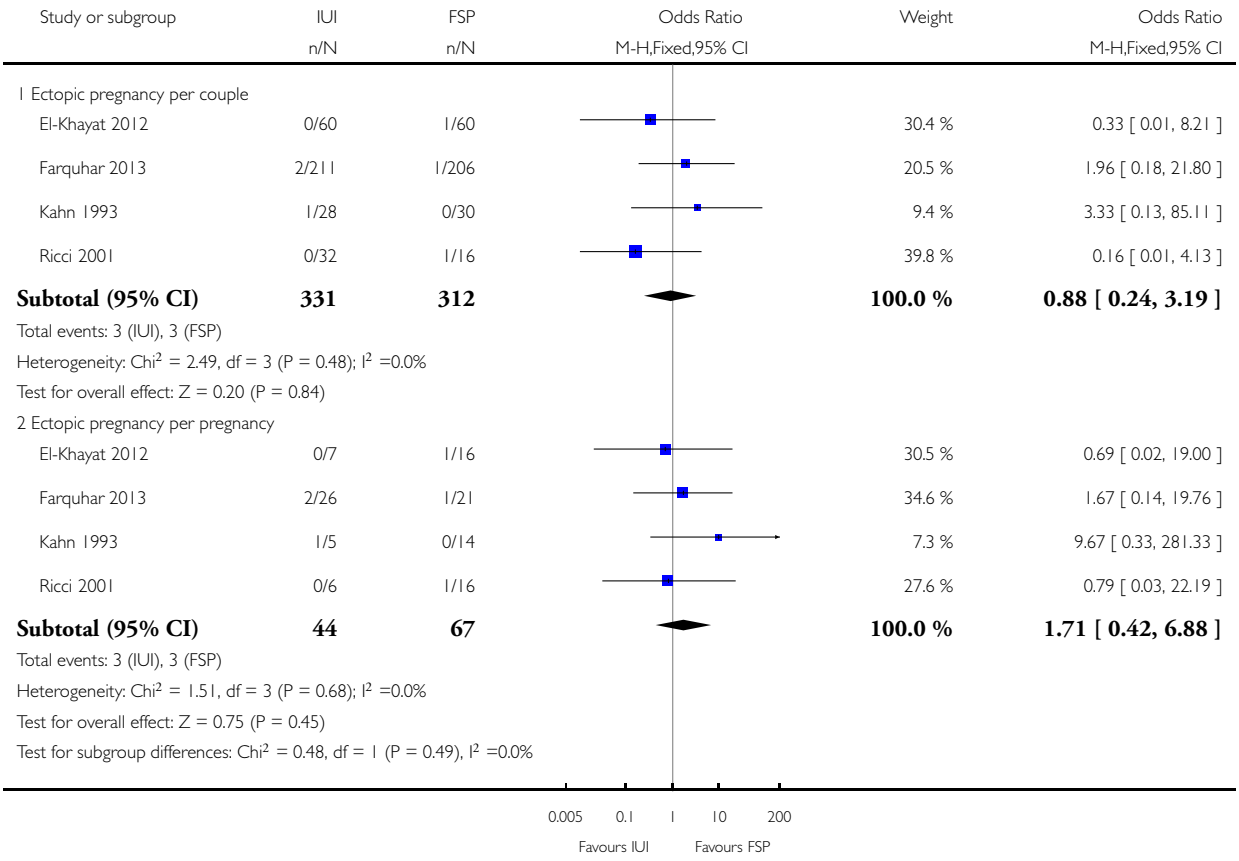


Analysis 1.5. Comparison 1 IUI versus FSP, Outcome 5 Ectopic pregnancy.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 IUI versus FSP

Outcome: 5 Ectopic pregnancy



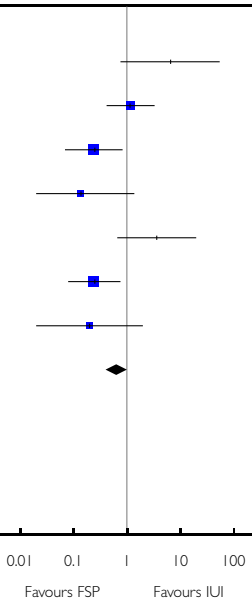
Analysis 2.1. Comparison 2 IUI versus FSP subgroups by indication, Outcome 1 Unexplained subfertility.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 2 IUI versus FSP subgroups by indication

Outcome: 1 Unexplained subfertility

Study or subgroup	IUI n/N	FSP n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clinical pregnancy					
Biacchiardi 2004 (1)	8/34	1/22		2.2 %	6.46 [0.75, 55.86]
Gregoriou 1995	12/30	11/30		15.7 %	1.15 [0.41, 3.26]
Kahn 1993	5/28	14/30		26.4 %	0.25 [0.07, 0.83]
Noci 2007	1/16	6/19		12.2 %	0.14 [0.02, 1.36]
Nuojua-Huttunen 1997	6/26	2/26		3.7 %	3.60 [0.65, 19.84]
Ricci 2001	6/32	16/33		30.4 %	0.25 [0.08, 0.75]
Trout 1999	1/27	4/25		9.5 %	0.20 [0.02, 1.95]
Total (95% CI)	**193**	**185**		**100.0 %**	**0.63 [0.39, 1.02]**
Total events: 39 (IUI), 54 (FSP)					
Heterogeneity: Chi^2 = 17.42, df = 6 (P = 0.01); I^2 =66%					
Test for overall effect: Z = 1.88 (P = 0.060)					
Test for subgroup differences: Not applicable					



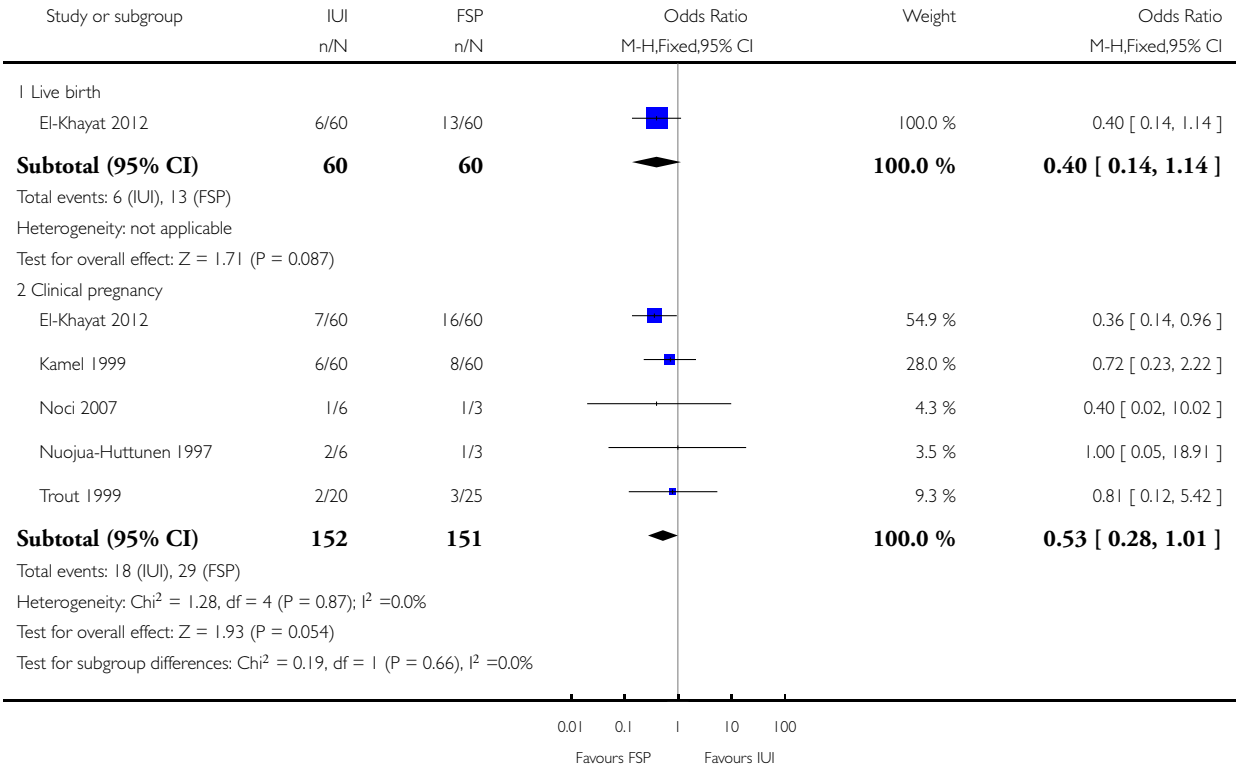
(1) Pre cross-over data

Analysis 2.2. Comparison 2 IUI versus FSP subgroups by indication, Outcome 2 Mild to moderate male factor subfertility.

Review: Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 2 IUI versus FSP subgroups by indication

Outcome: 2 Mild to moderate male factor subfertility



ADDITIONAL TABLES

Table 1. Per cycle data

Study	Clinical pregnancy per cycle		
	IUI	FSP	P value
Fanchin 1995	10/50 (20%)	20/50 (40%)	P < 0.04
Filer 1996	12/59 (20%)	5/47 (11%)	P > 0.05

APPENDICES

Appendix 1. MEDLINE

1 Insemination, Artificial/ (6821)
2 (intrauter$ adj5 inseminat$).tw. (1194)
3 (intra-uter$ adj5 inseminat$).tw. (131)
4 IUI.tw. (703)
5 or/1-4 (7614)
6 fallopian tube sperm perfusion.tw. (19)
7 FSP.tw. (446)
8 (Fallopian adj5 sperm$).tw. (97)
9 (tub$ adj5 sperm$).tw. (1868)
10 sperm$ flush$.tw. (7)
11 or/6-10 (2326)
12 5 and 11 (80)
13 randomised controlled trial.pt. (234274)
14 controlled clinical trial.pt. (74820)
15 Randomized Controlled Trials/ (48327)
16 Random allocation/ (57750)
17 Double-blind method/ (91028)
18 Single-blind method/ (10880)
19 or/13-18 (397294)
20 clinical trial.pt. (435392)
21 exp clinical trials/ (190560)
22 (clin$ adj25 trial$).ti,ab,sh. (129372)
23 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (90362)
24 Placebos/ (26128)
25 placebo$.ti,ab,sh. (114490)
26 random$.ti,ab,sh. (490003)
27 Research design/ (47276)
28 or/20-27 (866440)
29 animal/ not (human/ and animal/) (3095759)
30 19 or 28 (873731)
31 30 not 29 (800552)
32 12 and 31 (23)
33 (2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed. (3111083)
34 32 and 33 (5)
35 from 34 keep 1-5 (5)

Appendix 2. CENTRAL

1 Insemination, Artificial/ (112)
2 (intrauter$ adj5 inseminat$).tw. (290)
3 (intra-uter$ adj5 inseminat$).tw. (22)
4 IUI.tw. (206)
5 or/1-4 (378)
6 fallopian tube sperm perfusion.tw. (21)
7 FSP.tw. (30)
8 (Fallopian adj5 sperm$).tw. (29)
9 (tub$ adj5 sperm$).tw. (47)
10 sperm$ flush$.tw. (0)
11 or/6-10 (70)
12 5 and 11 (30)

13 from 12 keep 1-30 (30)

Appendix 3. CINAHL

1 Insemination, Artificial/ (163)
2 (intrauter$ adj5 inseminat$).tw. (30)
3 (intra-uter$ adj5 inseminat$).tw. (4)
4 IUI.tw. (16)
5 or/1-4 (178)
6 fallopian tube sperm perfusion.tw. (2)
7 FSP.tw. (17)
8 (Fallopian adj5 sperm$).tw. (2)
9 (tub$ adj5 sperm$).tw. (7)
10 sperm$ flush$.tw. (0)
11 or/6-10 (22)
12 5 and 11 (2)
13 exp clinical trials/ (43714)
14 Clinical trial.pt. (20712)
15 (clinic$ adj trial$1).tw. (10227)
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6114)
17 Randomi?ed control$ trial$.tw. (8946)
18 Random assignment/ (15159)
19 Random$ allocat$.tw. (1023)
20 Placebo$.tw. (8559)
21 Placebos/ (3489)
22 Quantitative studies/ (3196)
23 Allocat$ random$.tw. (60)
24 or/13-23 (61301)
25 12 and 24 (2)
26 from 25 keep 1-2 (2)

Appendix 4. EMBASE

1 fallopian tube sperm perfusion.tw. (22)
2 FSP.tw. (345)
3 (Fallopian adj5 sperm$).tw. (80)
4 (tub$ adj5 sperm$).tw. (1383)
5 sperm$ flush$.tw. (5)
6 or/1-5 (1737)
7 exp Artificial Insemination/ (3671)
8 (intrauter$ adj5 inseminat$).tw. (1172)
9 (intra-uter$ adj5 inseminat$).tw. (129)
10 IUI.tw. (737)
11 or/7-10 (4753)
12 6 and 11 (74)
13 Controlled study/ or randomised controlled trial/ (2405316)
14 double blind procedure/ (63789)
15 single blind procedure/ (6559)
16 crossover procedure/ (18585)
17 drug comparison/ (81250)
18 placebo/ (97915)
19 random$.ti,ab,hw,tn,mf. (367123)
20 latin square.ti,ab,hw,tn,mf. (1064)

21 crossover.ti,ab,hw,tn,mf. (32554)
22 cross-over.ti,ab,hw,tn,mf. (11275)
23 placebo$.ti,ab,hw,tn,mf. (146355)
24 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (106285)
25 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5769)
26 (clinical adj5 trial$).ti,ab,hw,tn,mf. (483066)
27 or/13-26 (2886258)
28 nonhuman/ (2878264)
29 animal/ not (human/ and animal/) (12847)
30 or/28-29 (2881866)
31 27 not 30 (1695407)
32 12 and 31 (28)
33 (2003$ or 2004$ or 2005$ or 2006$ or 2007$).em. (2449289)
34 32 and 33 (6)
35 from 34 keep 1-6 (6)

Appendix 5. Data collected

Types of participant

- What was the duration of subfertility?
- Were prognostic factors such as the age of the woman and the duration of subfertility considered?
- Were female factors excluded or corrected? All women had to have regular menstrual cycles with biphasic body temperature charts or normal luteal progesterone; patent tubes on hysterosalpingography (HSG) or laparoscopy; no cervical factors, thus a positive post-coital test or normal cervical mucus with pH > 6.3 and Insler score > 11.
- Had treatments been applied previously? Was it tubal surgery, controlled ovarian hyperstimulation without insemination, or other?

Types of intervention

- What method of controlled ovarian hyperstimulation (COH) was used?
- Were criteria to cancel the insemination because of the risk of multiple pregnancies or ovarian hyperstimulation syndrome (cancellation criteria) described?
- Duration of treatment: How many treatment cycles were offered?
- How many inseminations were performed per cycle?
- What timing method was used in natural cycles: with luteinising hormone (LH) in blood or urine?
- What timing method was used in cycles with COH. When no GnRHa was used: Was LH also measured in cycles with COH?
- What was the actual timing of IUI or FSP? Was IUI or FSP in natural cycles performed 20 to 40 hours after the onset of the LH surge was detected, and in cycles with COH 35 to 45 hours after hCG?
- Which semen was inseminated (donor semen or partner semen)?
- What method of semen preparation was applied?
- What were the semen characteristics before and after sperm processing (especially the number of motile spermatozoa that were inseminated)?

Types of outcome measure

· ***Primary outcome***

- Number of live births

· ***Secondary outcomes***

- Number of clinical pregnancies
- Number of multiple pregnancies

- Spontaneous abortion rate
- Number of tubal pregnancies

WHAT'S NEW

Last assessed as up-to-date: 12 September 2013.

Date	Event	Description
12 September 2013	New search has been performed	New search, September 2013. Added five RCTs: El-Khayat 2012; Farquhar 2013; Furuya 2010 (new RCTs); Noci 2007; Kamel 1999 (previously classified as awaiting assessment). Added one RCT to awaiting assessment section: Ricci 2008.
12 September 2013	New citation required but conclusions have not changed	There has been no change to the conclusions of this review

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2004

Date	Event	Description
11 February 2009	New citation required but conclusions have not changed	Review updated Dec 2007
1 October 2008	New search has been performed	Search revised and re-run; new study added (Ng et al 2003) and two studies waiting for assessment
3 June 2008	Amended	Converted to new review format.
6 December 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AEP Cantineau did the literature search and selected relevant trials for inclusion in the review. She also performed the statistical analyses and wrote the bulk of the results and discussion section. She analysed articles for the update of the review, updated the review in 2008 and advised on the structure, text and interpretation of the 2013 draft of the review.

MJ Heineman was the second review author for selection of relevant trials for inclusion. For the update, he analysed the selected articles. He also contributed to drafts of the review.

BJ Cohlen together with JH Evers and H Al-Inany took the lead in writing the original protocol for this review, was the third review author and resolved any disagreements between the first two review authors. He also contributed to drafts of the review and contributed to the update of the review.

C Farquhar selected the studies, extracted the data and advised on the structure, text and interpretation of the 2013 draft of the review.

J Marjoribanks selected the studies, extracted the data and drafted the 2013 update of the review.

DECLARATIONS OF INTEREST

Cindy Farquar is principal investigator of one of the included studies (Farquhar 2013).

SOURCES OF SUPPORT

Internal sources

- Isala Clinics, Zwolle, Netherlands.

Visit congress meetings to present results of review

- The Cochrane Collaboration, New Zealand.

Technical support

- University Medical Centre, Groningen, Netherlands.

Technical support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2013 update.

- Methods were updated in accordance with current Cochrane methodological standards.
- Participant inclusion criteria were widened to “non-tubal infertility”.
- OHSS was deleted as an outcome.
- Sensitivity analysis was conducted for clinical pregnancy rather than live birth because only three studies reported live birth.
- Both per-couple (main analysis) and per-pregnancy (sensitivity analysis) analyses were conducted for multiple pregnancy, miscarriage and ectopic pregnancy.
- A random-effects model was used if substantial heterogeneity was detected (I^2 > 50%).

INDEX TERMS

Medical Subject Headings (MeSH)

*Fallopian Tubes; *Pregnancy Outcome; *Reproductive Techniques, Assisted; Gamete Intrafallopian Transfer [methods]; Infertility, Female; Live Birth; Randomized Controlled Trials as Topic; Sperm Count

MeSH check words

Female; Humans; Pregnancy